

New Biological Therapies for Asthma: Do the Benefits Justify the Cost?

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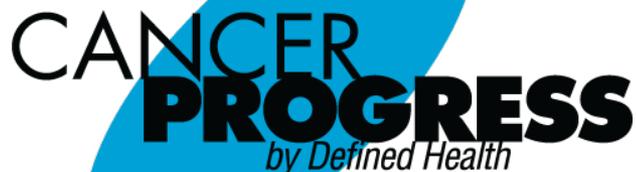


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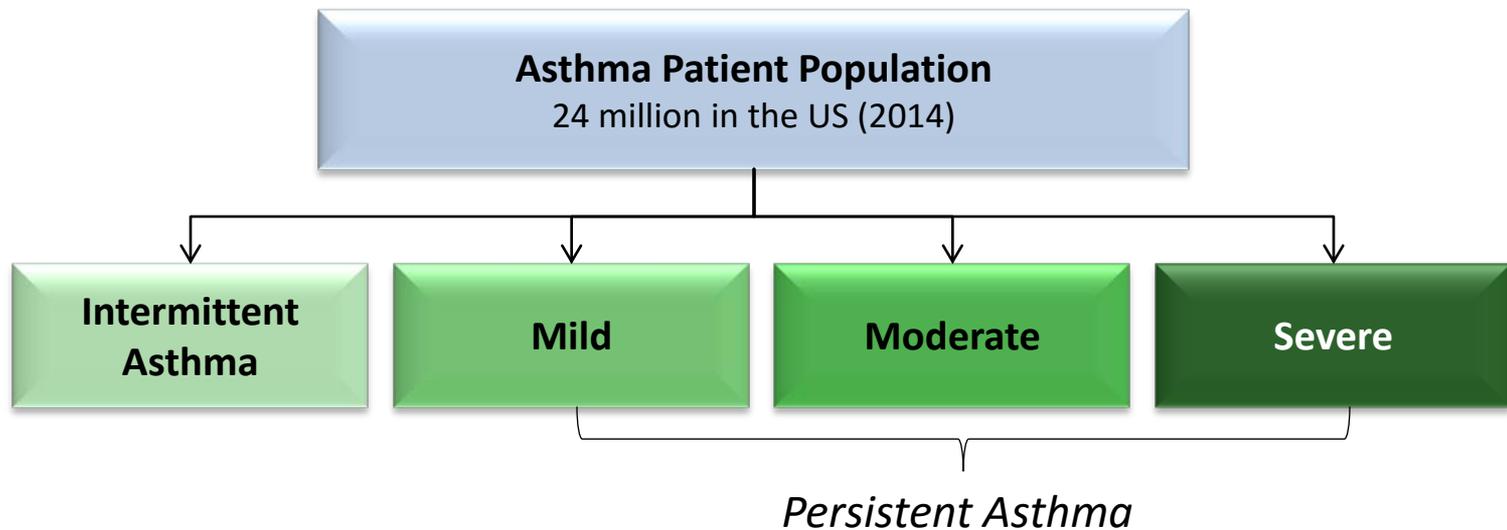
BioEurope Spring 2017
March 20 – 22, 2017
Barcelona, Spain
www.therapeuticinsight.com

Defined Health will also be participating in the following industry events:

ASCO | June 3 - 7, 2016 | Chicago IL | <http://dfndhlth.com/ASCO-2016>
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Oncology Market Access & Pricing 2016 | June, 16 - 17, 2016 | Philadelphia, PA | <http://dfndhlth.com/OMAP-2016>
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SITC 2016 | November 9 – 13, 2016 | National Harbor, MD | <http://dfndhlth.com/SITC-2016>
ASH Annual Meeting | December 3 - 6, 2016 | San Diego, CA | <http://dfndhlth.com/ASH-2016>

Asthma is a Highly Prevalent Disease

- ◆ 300 million people worldwide and 24 million or 8% of the US population are affected by asthma, and the prevalence is expected to grow over the next decade.
- ◆ Asthma is a chronic lung disease that often starts in childhood and is characterized by repeated episodes of wheezing, breathlessness, chest tightness, and nighttime or early morning coughing.
- ◆ **The asthma patient population is segmented based on disease severity:**



Center for Disease Control, National Health Interview Survey Data, 2014; Cowen and Company, Mar 2016

Asthma is Associated with Significant Healthcare Cost

- ◆ *In the US*, 1.8 million people visited an ER department for asthma-related care in 2010, and 439,000 people were hospitalized due to asthma.
- ◆ The yearly burden of asthma is ~\$56 billion, and majority of it is direct cost, with hospital stay being the biggest cost driver.
- ◆ **Severe asthma accounts for an estimated 60% of the associated healthcare costs.**

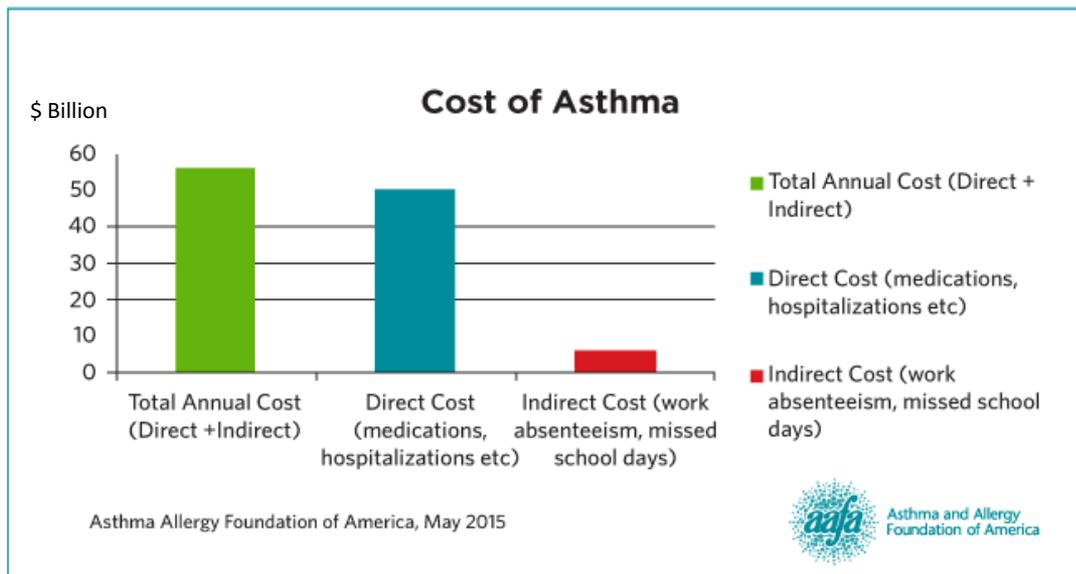


Figure 1. Formulary decision makers at MCOs cited hospitalizations as the primary contributor to the economic impact of asthma, followed closely by emergency department visits and prescription drugs.

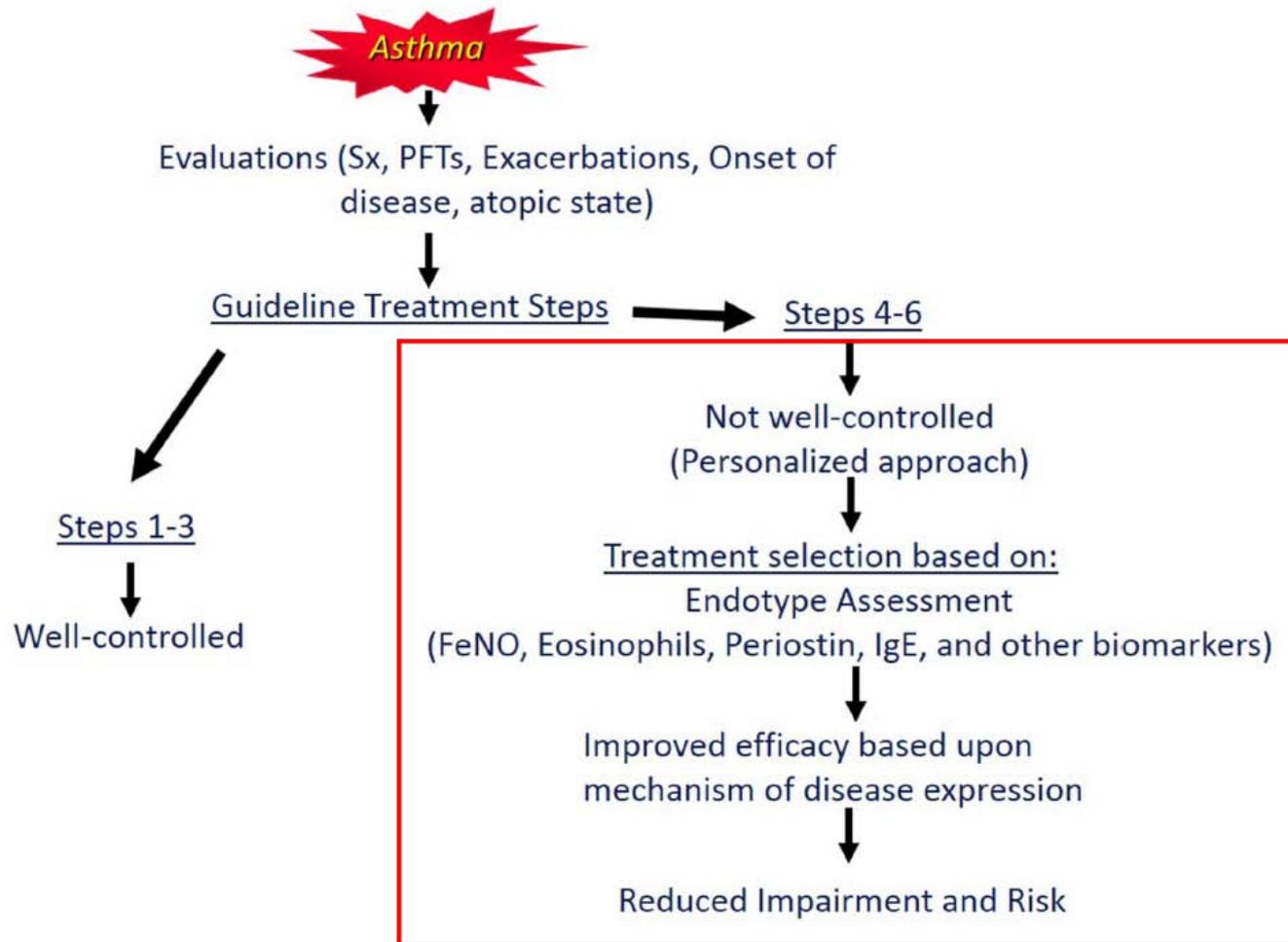
At Present, Relatively Inexpensive Inhalation Therapies Dominate the Asthma Category

- ◆ According to the NHLBI guidelines, current treatment of asthma involves a stepwise approach.
- ◆ **Vast majority of mild-moderate asthma patients can be adequately managed and well-controlled on relatively inexpensive inhalation therapies;** ~5 major pharmacological classes (short- and long-acting bronchodilators, inhaled corticosteroids, anti-cholinergics, leukotriene modifiers).

		STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6	
≥12 years of age	Preferred Treatment [†]	SABA* as needed	low-dose ICS*	low-dose ICS* + LABA* OR medium-dose ICS*	medium-dose ICS* + LABA*	high-dose ICS* + LABA* AND consider omalizumab for patients who have allergies ^{††}	high-dose ICS* + LABA* + oral corticosteroid ^{§§} AND consider omalizumab for patients who have allergies ^{††}	
	Alternative Treatment ^{†,‡}		cromolyn, LTRA,* or theophylline [§]	low-dose ICS* + either LTRA,* theophylline, [§] or zileuton ^{‡‡}	medium-dose ICS* + either LTRA,* theophylline, [§] or zileuton ^{‡‡}			
		Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma.**						
Quick-Relief Medication		<ul style="list-style-type: none"> ▪ SABA* as needed for symptoms. The intensity of treatment depends on severity of symptoms: up to 3 treatments every 20 minutes as needed. Short course of oral systemic corticosteroids may be needed. ▪ Caution: Use of SABA >2 days/week for symptom relief (not to prevent EIB*) generally indicates inadequate control and the need to step up treatment. 						

NIH, National Heart, Lung and Blood Institute (NHLBI), 2007

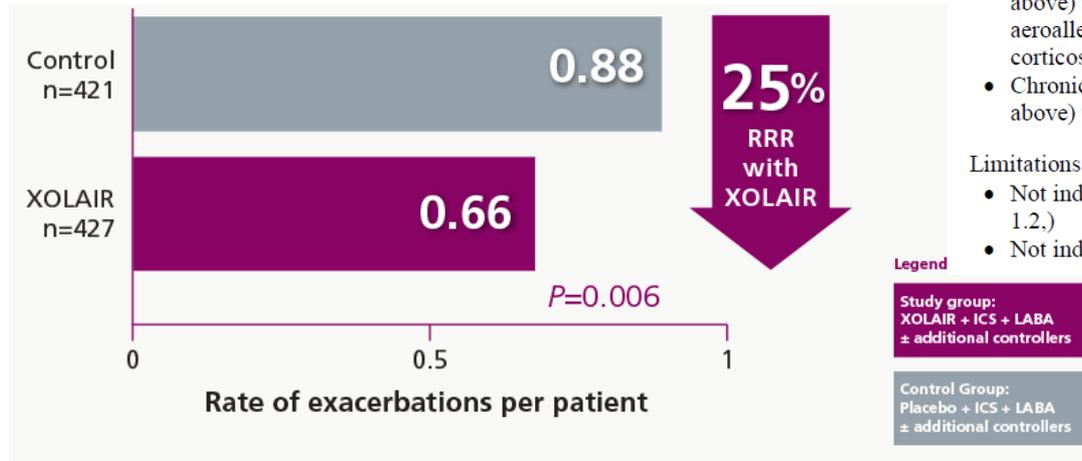
Evolving 2013 Guidelines Suggest a Personalized, Evidence-based Approach for Treatment of Uncontrolled Asthma



J Allergy Clin Immunol Pract. 2015 ; 3(2): 152–161; 2013 ERS/ATS guidelines

Until 2015, Xolair was the Only Approved Biologic for Asthma

- ◆ Xolair (omalizumab, Roche/Novartis) is an anti-IgE antibody approved in 2003 for treatment of moderate to severe persistent allergic asthma in patients 12 years and older.
 - 100K patients are treated WW with ~50% of the patients in the US
 - \$24K/\$15K per year in the US and ex-US
 - Global sales around \$1.9B in 2015
- ◆ Use limited by a combination of biomarker selection criteria, weight-based / IgE based dosing and reimbursement restrictions. Its efficacy varies considerably by biomarker specified subgroup.



INDICATIONS AND USAGE

Xolair is an anti-IgE antibody indicated for:

- Moderate to severe persistent asthma in patients (12 years of age and above) with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids (1.1)
- Chronic idiopathic urticaria in adults and adolescents (12 years of age and above) who remain symptomatic despite H1 antihistamine treatment (1.2)

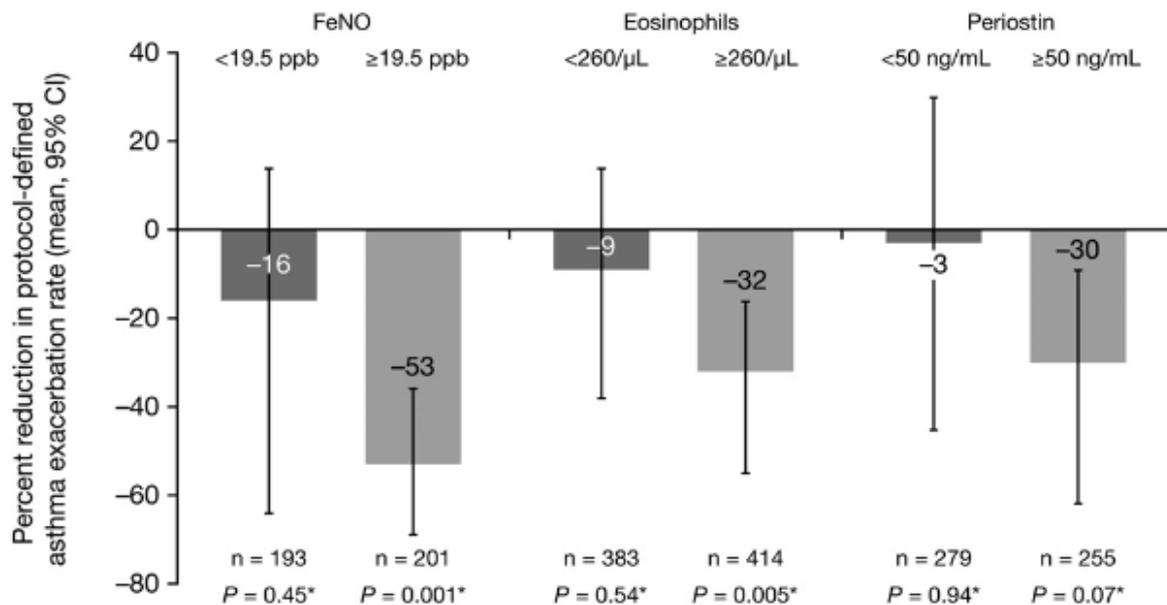
Limitations of use:

- Not indicated for other allergic conditions or other forms of urticaria. (1.1, 1.2.)
- Not indicated for acute bronchospasm or status asthmaticus. (1.1, 5.3)

<http://www.xolair.com>

Omalizumab EXTRA Study – Exacerbations in Biomarker Specified Subgroups of Uncontrolled Severe Persistent Asthma

Effects of Omalizumab in Allergic Asthma within biomarker specified subgroups

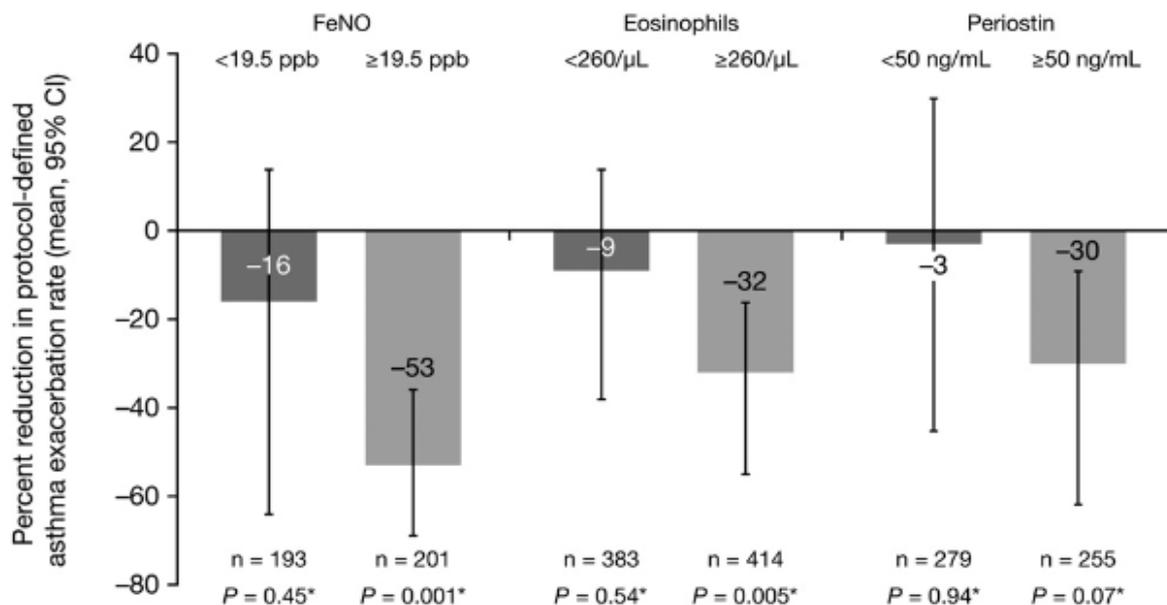


	Exacerbation rates					
	Low FeNO at baseline	High FeNO at baseline	Low eosinophils at baseline	High eosinophils at baseline	Low periostin at baseline	High periostin at baseline
Omalizumab	0.60	0.50	0.65	0.70	0.73	0.66
Placebo	0.71	1.07	0.72	1.03	0.72	0.93

Am J Respir Crit Care Med 2013;187(8):804-811

Omalizumab EXTRA Study – Exacerbations in Biomarker Specified Subgroups of Uncontrolled Severe Persistent Asthma

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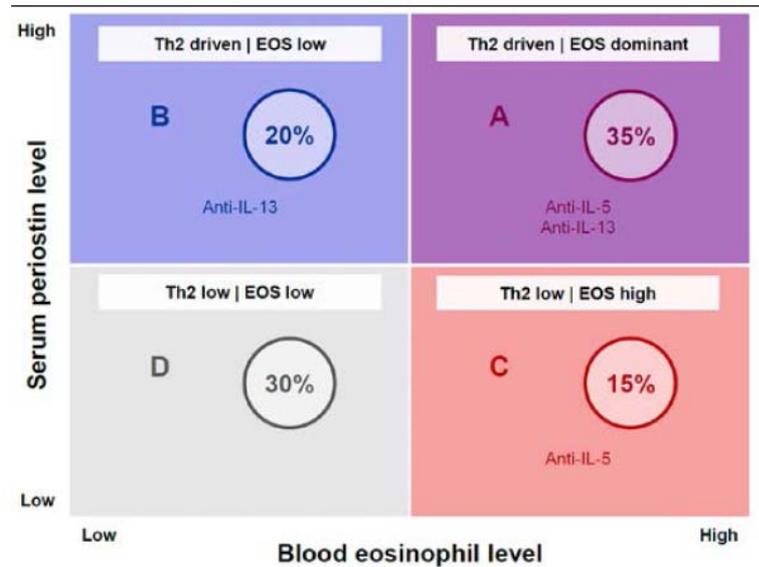


Exacerbation rates						
	Low FeNO at baseline	High FeNO at baseline	Low eosinophils at baseline	High eosinophils at baseline	Low periostin at baseline	High periostin at baseline
Omaliuzumab	0.60	0.50	0.65	0.70	0.73	0.66
Placebo	0.71	1.07	0.72	1.03	0.72	0.93

Asthma Biologics Focused on a Limited Set of Mechanisms and Target a Small Subset of Patients with Overlapping Phenotypes

- ◆ The high level of unmet need in severe asthma and research breakthroughs surrounding the role of inflammatory cytokines in asthma pathophysiology have spurred the development of multiple cytokine-inhibiting agents that target Th2 and eosinophil (EOS)-driven phenotypes, and are expected to be used in biomarker selected populations.
- ◆ However, there is significant overlap between the addressable patient populations with little guidance or validated biomarkers to suggest which patients will benefit.

Potential Treatment Paradigm For Severe Asthma



- High EOS present in 40-60% of severe asthmatics; however, significant overlap between elevated EOS and IgE (Xolair candidates);
- Elevated periostin is also associated with Th2 phenotype; 85% of periostin high patients also have EOS phenotype but not all EOS patients have high periostin

Allergy 2015; DOI: 10.1111/all.12580; NHLBI Expert Panel Report; Cowen and Company; March 2016; ; Image source AstraZeneca

Extent of Unmet Need in Uncontrolled Asthma Complicated by Poor Adherence to Inhalation Therapy

- ◆ Estimating the severe asthma patient population is challenging – the current estimates range between 5-25% for patients who remain uncontrolled despite the use of high dose inhaled corticosteroids plus a second controller medication (e.g., LABA), and these patients also often rely on long-term oral steroids.
- ◆ Patient adherence with inhalation therapy is quite poor which complicates the ability to assess treatment response, and it also presents a challenge in justifying the use of asthma biologics.
 - ~55% of adults and 78% of children do not strictly comply with their prescribed inhalation therapy
- ◆ Nevertheless, it is generally assumed that ***less than half of the asthma patients with uncontrolled disease may in fact be candidates for additional treatments with biologics.*** Therefore, payers are increasingly likely to require documentation that patient strictly follow adherence requirements prior to authorization of a biologic.

First Two in a Series of New Biologics Recently Approved

- ◆ Nucala (mepolizumab, GSK) is the first anti-interleukin 5 (IL-5) monoclonal antibody approved for treatment of severe eosinophilic asthma. It was recently launched in the US in January of 2016.
- ◆ Cinqair (reslizumab, Teva) is also an anti-IL-5 approved in March 2016. It is expected to launch in the US in 2Q 2016 and currently being reviewed by the EMA.

Drug Company	Target Patient Population	Dosing
Nucala GSK	Patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype (>300 cells/mCL)	Subcutaneous (SC)
Cinqair Teva	Treatment of inadequately controlled severe eosinophilic asthma (>400 cells/mCL)	Intravenous infusion, SC expected in 2018

Company Websites

Other Biologics in Development for Severe Asthma in Phase 3

Drug Company	Mechanism	Patient Population	Efficacy Data
Benralizumab AZN	Anti-IL-5	<ul style="list-style-type: none"> Uncontrolled eosinophilic asthma (>300 cells/mCL) 	<ul style="list-style-type: none"> Met the primary endpoint in 2 pivotal Phase 3 studies; US and EU regulatory submissions expected 2H 2016; 43-57% reduction in exacerbations, depending on the dose and baseline blood eosinophil level; Decreased blood eosinophil counts to low levels after the first dose (Phase 2b data)
Tralokinumab AZN	Anti-IL-13	<ul style="list-style-type: none"> severe uncontrolled asthma High Periostin 	<ul style="list-style-type: none"> 67% reduction in asthma exacerbations (Phase 2b data); Phase 3 data expected in 2017
Lebrikizumab Roche	Anti-IL-13	<ul style="list-style-type: none"> Severe uncontrolled asthma despite high dose ICS+ second controller medication 	<ul style="list-style-type: none"> Mixed top-line results from two <i>identical</i> Ph 3 studies -- significant reduction in exacerbations and improvement in FEV1 in patients with high periostin or blood eosinophils (LAVOLTA I) but no statistical significance observed in (LAVOLTA II) with the rate of asthma exacerbations over 52 weeks as the 1 endpoint in both studies. Strong Phase 2 data (60% reduction in exacerbation vs. 5% placebo in periostin high patients; FEV1 increased 9% in high periostin group vs. placebo compared to 2.6% improvement vs. placebo in the low periostin group)
Dupilumab Regeneron	Anti-IL-4/ IL-13	<ul style="list-style-type: none"> Moderate to severe uncontrolled eosinophilic asthma 	<ul style="list-style-type: none"> Phase 2b study met its primary endpoint of improving lung function; 64-75% reduction in exacerbations compared to placebo; Phase 3 data expected in 2017

1. Company Press Releases; 2. ClinicalTrials.gov

Pricing of Nucala Already Creating Controversy

GSK's new \$32,500 asthma med costs at least 2X too much, U.S. pricing watchdog says

GlaxoSmithKline (GSK) has a new drug that's tailored for patients with a specific type of severe asthma. But according to a nonprofit body that evaluates drugs' prices against their clinical effectiveness, it costs far, far too much.



Nucala, an injectable indicated for severe asthma patients with

eosinophilic inflammation, should cost between \$7,800 and \$12,000 per year, according to an analysis by the Institute for Clinical and Economic Review (ICER). That's as much as 76% lower than the \$32,500 tag it bears right now.

ICER doesn't argue that Nucala, administered once per month, is not effective. "There is moderate certainty" that adding it to the current standard of care achieves results as good or better than the standard of care on its own, it said in a draft report. Nucala also cuts the need for oral steroids, which can prove highly toxic if taken at high doses for long periods of time.

But thanks to short clinical trials for Nucala, ICER isn't sure just how long the med's benefits will last. "There is uncertainty" about whether they'll "persist over the long term," it wrote.

Nucala Broadly Indicated for Severe Asthma with Eosinophilic Phenotype

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NUCALA[®] safely and effectively. See full prescribing information for NUCALA.

NUCALA (mepolizumab) for injection, for subcutaneous use
Initial U.S. Approval: 2015

INDICATIONS AND USAGE

NUCALA is an interleukin-5 antagonist monoclonal antibody (IgG1 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. (1)

Limitations of Use:

- Not for treatment of other eosinophilic conditions. (1)
- Not for relief of acute bronchospasm or status asthmaticus. (1)

DOSAGE AND ADMINISTRATION

100 mg administered subcutaneously once every 4 weeks. (2)

- See Full Prescribing Information for instructions on reconstitution of lyophilized powder, and preparation and administration of the injection.

DOSAGE FORMS AND STRENGTHS

For injection: 100 mg of lyophilized powder in a single-dose vial for reconstitution. (3)

CONTRAINDICATIONS

History of hypersensitivity to mepolizumab or excipients in the formulation. (4)

But Payers are Requiring Stringent Documentation of Patient History and Medication Use for Prior-Authorization of Biologics

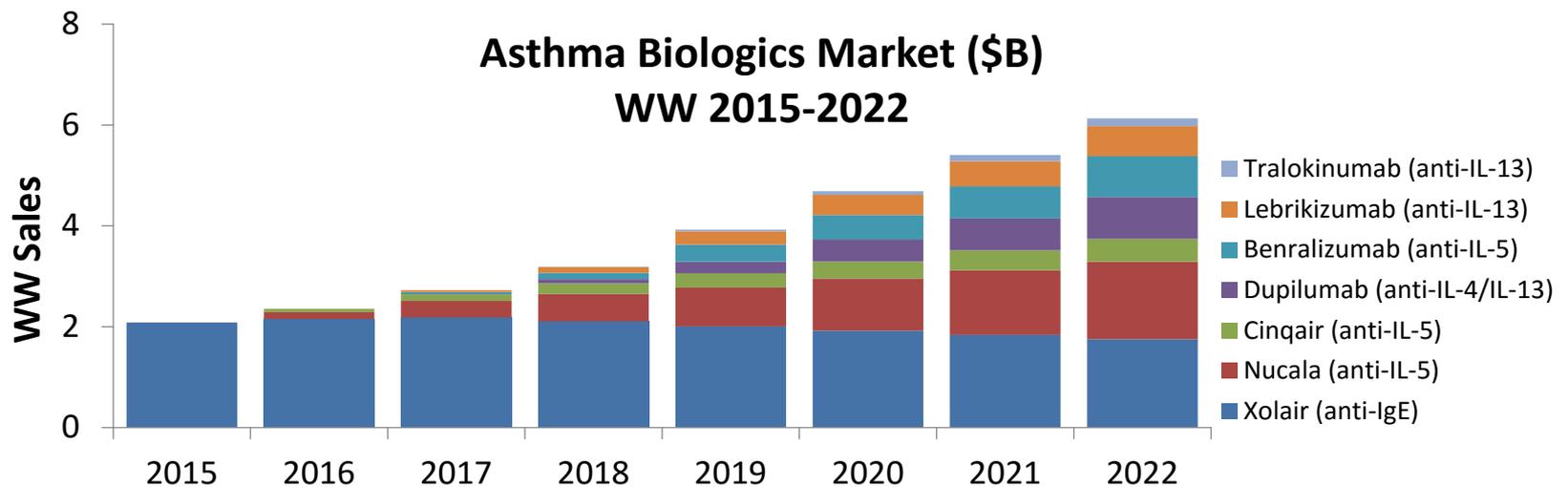
- ◆ Nucala is considered medically necessary for the add-on maintenance treatment of persons with severe asthma aged 12 years and older who meet the following criteria:

- **Persistent airflow obstruction** as indicated by FEV1; *and*
 - **Evidence of asthma, as indicated by FEV1 reversibility** of at least 12% and 200ml after albuterol (salbutamol) administration; *and*
 - **Eosinophilic asthma phenotype, as determined by blood eosinophils** ; *and*
- **Previously confirmed history of ≥ 2 exacerbations requiring treatment with systemic steroids** in the 12 months prior to initiation of mepolizumab, despite the use of high-dose ICS; *and*
 - **History of 2 or more exacerbations in the previous year *despite regular use of high-dose inhaled corticosteroids with oral corticosteroids*** for at least 6 months or high-dose ICS without oral corticosteroids for at least 12 months; *and*
 - **Current treatment with an additional controller medication, besides ICS, for at least 3 months or a documented failure** in the past 12 months of an additional controller medication for at least 3 successive months; *and*
- ◆ Continued use of Nucala is considered medically necessary for persons who have evidence of improvement, as indicated by reduction in frequency of exacerbations, reduced use of controller medications, reduction in asthma symptoms, or increase in FEV1 from pretreatment baseline.

http://www.aetna.com/cpb/medical/data/800_899/0897.html

Future Outlook for Asthma Biologics

- ◆ Two new asthma biologics (Nucala and Cinqair) have now been approved, and positive Phase 3 trial read-outs expected for other late-stage anti-cytokine biologics in the near future. However, the actual sales for Nucala has been lower than anticipated with \$12M in sales for Q4 2015-Q1 2016.
- ◆ We also expect slow uptake of these novel asthma biologics due to empirical use, high cost of therapy, and stringent prior-authorization requirements for reimbursement.
- ◆ According to current estimates, the asthma biologics may generate approx. \$6B in WW sales in 2022, but this may be an overestimation as it does not sufficiently account for biomarker driven selection of these agents within a small subset of ~5-10% of asthma patients with overlapping phenotypes.



EvaluatePharma, 2016

Discrepancy Between Company Forecasts & Analyst Projections

FirstWord

PHARMA

Where People Who Know First Go First.

AstraZeneca's benralizumab hits main goal of two late-stage asthma studies

By Matthew Dennis
Created 05/17/2016 - 04:31

AstraZeneca announced Tuesday that the experimental drug benralizumab met the primary endpoint in two pivotal Phase III studies, demonstrating significant reductions in the annual asthma exacerbation rate compared to placebo. The company noted that US and European regulatory submissions for the biologic therapy, which is in-licensed from Kyowa Hakko Kirin's BioWa unit, are expected in the second half of the year.

The SIROCCO and CALIMA trials included a total of 2511 patients and evaluated benralizumab as an add-on therapy for severe uncontrolled asthma with eosinophilic inflammation in adults and adolescents 12 years of age and older. Subjects were randomised to receive benralizumab dosed either every four weeks or every four weeks for the first three doses followed by every eight weeks, or placebo.

AstraZeneca noted that the primary analysis population of the studies included patients on high-dose inhaled corticosteroids plus long-acting beta2-agonist with a baseline blood eosinophil count of at least 300 cells per microliter. The company indicated that the safety and tolerability findings for benralizumab were generally consistent with those reported in previous trials. The drugmaker added that results from the SIROCCO and CALIMA trials will be presented at a future medical meeting.

Sean Bohlen, AstraZeneca's chief medical officer, said "we are pleased with the top-line results...as they demonstrate the potential for benralizumab to improve outcomes for patients with severe asthma." Bohlen added "benralizumab is AstraZeneca's first respiratory biologic and its development underscores our commitment to transform the treatment of asthma and chronic respiratory disease with our next generation of respiratory medicines."

Benralizumab is also being investigated in a Phase III programme for patients with severe chronic obstructive pulmonary disease. Although AstraZeneca forecasts that the drug will generate annual sales of \$2 billion, analysts estimate revenue of \$450 million by 2021.

For more information on drugs under development for asthma, see [Targeted Therapies In Asthma](#) [1].

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Dr. John Oppenheimer is the Director of Clinical Research at Pulmonary and Allergy Associates as well as Clinical Professor of Medicine at UMDNJ-Rutgers. He is board certified in Internal Medicine and Allergy and Immunology. He trained and was on faculty at the National Jewish Center in Denver Colorado. Dr. Oppenheimer has participated in over 100 clinical studies with over 100 publications. He serves as the Associate Editor of the *Annals of Allergy Asthma and Immunology*, co-section editor of *Current Reports of Allergy and Immunology* and serves as a reviewer for several journals including the *Journal of Allergy and Clinical Immunology* and *JAMA*. He is the past Chairman of the ADT section as well as the Interest Section Coordinating Committee of the AAAAI, serves on the Joint Task Force of the Practice Parameter Committee for Allergy Immunology, the writing committee of the cough guidelines committee for the American College of Chest Physicians, a voting member of PCPI and member of the measures development for atopic dermatitis, is on the Board of Directors of the American Board of Allergy and Immunology 2010-15 and is the past Chairman of the ABAI. He has focused his career on guideline development and has been actively involved in measurement development in the field of allergy and immunology.

Aruni S. Arachchige Don, PhD, Consultant, Defined Health



Aruni's client work encompasses opportunity assessments, therapeutic area growth strategy and search projects, as well as the identification and evaluation of partnering opportunities. Since joining Defined Health in 2013, Aruni has contributed to projects that span the therapeutic landscape, with special emphasis on projects in respiratory diseases.

Prior to Defined Health, Aruni conducted translational research on targeting mTOR signaling for treatment of CNS injuries (e.g., traumatic brain and spinal cord injuries) and cancer. She is a published author of 7 peer-reviewed articles, including an expert review (in collaboration with Dr. Wise Young, the Founding Director of the W.M. Keck Center for Collaborative Neuroscience and a world renowned neuroscientist in the field of spinal cord injury at Rutgers University). Aruni completed a 3-year postdoctoral fellowship from the New Jersey Commission on Spinal Cord Research. During her postdoctoral tenure, Aruni also interned at the Office of Technology Transfer and Business Development, where she was involved in various aspects of business development and licensing and developed proficiency in evaluation and identification of novel technologies appropriate for commercialization. She is knowledgeable in the areas of intellectual property and technology transfer, the drug development process and related regulatory issues.

Aruni received a PhD in Pharmacology from the University of Iowa, Carver College of Medicine. She also earned Bachelor of Science degrees in both Biology and Microbiology from the University of Wisconsin, Madison and from the University of Minnesota, Twin Cities.

Ed Saltzman, President, Defined Health



Ed is President and Founder of Defined Health. He possesses a vast knowledge of the pharmaceutical and biotechnology industry accumulated over Defined Health's 27 years of consultancy to pharma, biotech, specialty pharma and investors. From this unique perspective, he manages business development and disease area strategy projects and also provides guidance on most of Defined Health's project work.

Prior to founding Defined Health, Ed held positions at the Ayerst Laboratories unit of American Home Products, where he had responsibility for evaluation and forecasting of compounds being considered for licensing, and at FIND/SVP, where he managed the Healthcare Information Center.

Ed is a well regarded and in demand speaker on industry issues. He has spoken over the past 10 years to large audiences at Defined Health's Therapeutic Insight conferences, the Licensing Executives Society Annual Meeting and various industry conferences. In addition to these public events, Ed has presented targeted strategy briefings and held discussions privately with scores of boards of directors, executive management committees and licensing and business development teams at large pharma, specialty pharma and biotech companies. Ed is a member of the Licensing Executives Society and the New York Pharma Forum and is a graduate of New York University.